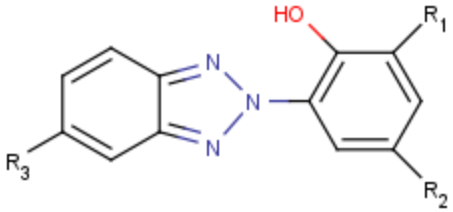
NTP
National Toxicology Program

Phenolic Benzotriazoles



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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
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National Institute of Environmental Health Sciences / National Institutes of Health
National Institute for Occupational Safety and Health / Centers for Disease Control
National Center for Toxicological Research / Food and Drug Administration

Nomination and Use

- Phenolic Benzotriazole (PBZT) class was nominated by NIEHS

- PBZTs are UV stabilizers (absorb UV to increase stability) and primarily used as industrial additives: paints and coatings, rubber and plastic products, and electrical and electronic products.

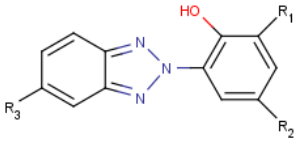
- Some PBZTs (e.g. Octrizole, Drometrizole, Bisoctrizole) are used in food contact polymers and adhesives, cosmetics, sunscreens, and fragrances (e.g. candles).

PBZT Production

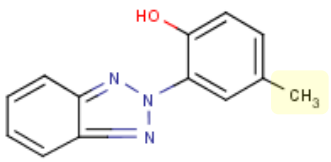
Name	CASRN	2006 IUR (lbs)	Log P*
Octrizole	3147-75-9	1 to < 10 million	7.4
DitPe-BZT	25973-55-1	1 to < 10 million	7.9
DiMeEtPh-BZT	70321-86-7	1 to < 10 million	9.2
tBuPrMeEst-BZT	84268-33-7	1 to < 10 million	5.7
Tbu(C7-9)Est-BZT	127519-17-9	1 to < 10 million	
Drometrizole	2440-22-4	500,000 to <1 million	4.3
Bumetrizole	3896-11-5	500,000 to <1 million	6.8
MeEtPhMeBu-BZT	73936-91-1	500,000 to <1 million	10
ditBu-ClBZT; DBHCB	3864-99-1	<500,000	7.5
Bisoctrizole	103597-45-1	<500,000	14

*Predicted LogP @ 25 C using Advanced Chemistry Development (ACD/Labs) Software V11.02 (©1994-2010 ACD/Labs)

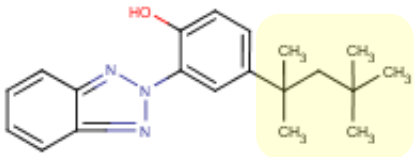
PBZT Class Structures



Single Subst.

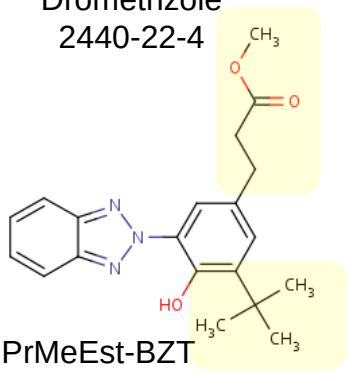


Drometrizole
2440-22-4

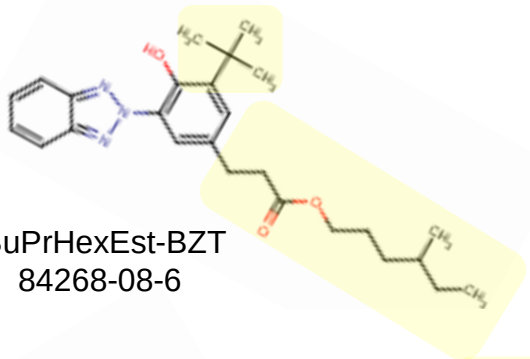


Octrizole
3147-75-9

Double w/ ester

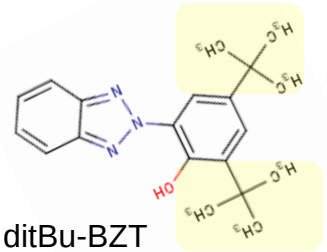


tBuPrMeEst-BZT
84268-33-7

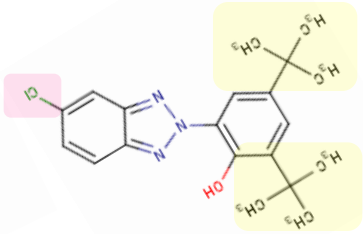


tBuPrHexEst-BZT
84268-08-6

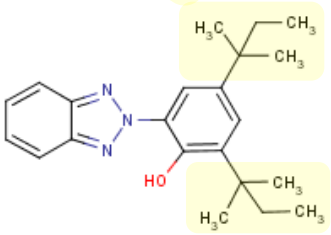
Double Subst.



ditBu-BZT
3846-71-7

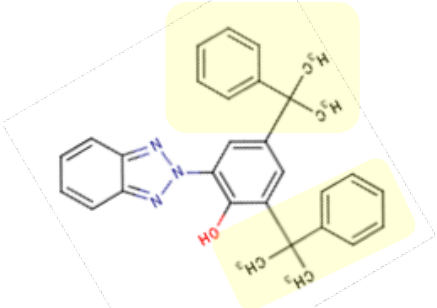


ditBu-ClBZT
3864-99-1

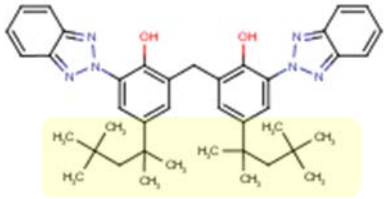


ditPe-BZT
25973-55-1

Other PBZTs



diMeEtPh-BZT
70321-86-7



Bisoctrizole
103597-45-1

PBZT Exposure

- PBZTs have low water solubility and low vapor pressure. Some thought to be environmentally persistent. Human exposure data lacking

- PBZTs measured in marine wildlife, seafood (ppt-ppb) and sediment/soil/sludge (ppt-ppm)

- Little PK/ADME data: Two ester linkage PBZTs had short half life in rat (10-12 hrs, n=2)

PBZT Toxicity Studies

Name	CASRN	10^6 lbs	Subchronic	Chronic	Repro	Prenatal
Octrizole	3147-75-9	1-10	R 30d			
DitPe-Bzt	25973-55-1	1-10	R/D 90d			
DiMeEtPh-BZT	70321-86-7	1-10	R 90d			R
tBuPrMeEst-BZT	84268-33-7	1-10	R 14d, 29d			
Tbu(C7-9)Est-BZT	127519-17-9	1-10				
Drometrizole	2440-22-4	0.5-1	R/D 90d	R/M	M (DL)	R/M
Bumetrizole	3896-11-5	0.5-1				
MeEtPhMeBu-BZT	73936-91-1	0.5-1				
ditBu-ClBZT	3864-99-1	<0.5	R 28d, 90d		R (421)	R
Bisoctrizole	103597-45-1	<0.5				
ditBu-BZT	3846-71-7	NA	R 28d,90d	R (1yr)		

R=rat; D=dog; M=mouse

PBZT Subchronic Studies

Name	CASRN	Study	Target Sites
Octrizole	3147-75-9	Rat 30d	None
DitPe-BZT	25973-55-1	Dog 90d	Liver, Kidney, M/F Repro Organs (M>F)
		Rat 90d	Liver, Kidney, Hematology (M>F)
DiMeEtPh-BZT	70321-86-7	Rat 90d	Liver
tBuPrMeEst-BZT	84268-33-7	Rat 14d, 29d	Liver
Drometrizole	2440-22-4	Dog 13 wk	Ovary weights
		Rat 13 wk	Liver, Kidney, Testes, Hematology
ditBu-ClBZT	3864-99-1	Rat 28d, 90d	Liver (M>F)
ditBu-BZT	3846-71-7	Rat 28d,90d	Liver, Hematology, Kidney, Spleen, Heart, Testes (M>F)

PBZT Reproductive/Development/Endocrine Toxicity

- Some PBZTs evaluated in vitro and in vivo for ER/AR activity - negative

- No comprehensive reproductive toxicity studies
  - ♂ mouse dominant lethal (Drometrizole) and rat OECD 421 (ditBu-ClBZT)
    - Decreased pup weights in OECD 421
  - Reproductive “hits” in subchronic studies (Drometrizole & DitPe-BZT)

- Prenatal developmental toxicity studies:
  - Drometrizole and ditBu-ClBZT were reported to be negative
  - DiMeEtPh-BZT: reduced fetal weight, delayed skeletal maturation at 1000 mg/kg; one high dose (3000 mg/kg) fetus showed omphalocele (failure of ventral closure), no maternal toxicity

PBZT Dermal Toxicity/Sensitivity

- Drometrizole
  - Negative in murine local lymph node assay (LLNA) when administered topically
  - No cross reaction (no increase in mouse ear thickness) with CAS# 70321-86-17, Bumetrizole, 3864-99-1, 25973-55-1, or Octrizole
- Octrizole
  - Repeat insult patch test on volunteers was negative for skin sensitization
- Bisoctrizole
  - Two case reports of reactions (dermatitis) with product containing bisoctrizole

PBZT Chronic Toxicity and Carcinogenic Activity

- Seven PBZTs were tested for genotoxicity and were negative
- Drometrizole two year feed exposure did not increase tumors:
  - 5, 50, 500 ppm exposure to SPF mice: no significant effects
  - 100, 300, 1000, 3000 ppm exposure to CFY rats: reduced weight gain
- ditBu-BZT one year gavage exposure:
  - 0.1, 0.5, 2.5 mg/kg to male rats: liver, hematology, body weight
  - 0.5, 2.5, 12.5 mg/kg to female rats: liver, hematology (12.5 mg/kg)
- 1H-Benzotriazole (NCI 1978, NTP Technical report # 88)
  - 6700, 12100 ppm to rats: hepatocellular adenomas (not clearly associated); brain tumors (equivocal)
  - 11700, 23500 ppm to mice: alveolar/bronchiolar carcinomas in females (not clearly associated)

Key Issues

- Identifying which chemicals in the PBZT class should undergo toxicity evaluation

- Identifying specific chemicals with the highest potential for hazard and/or internal exposure

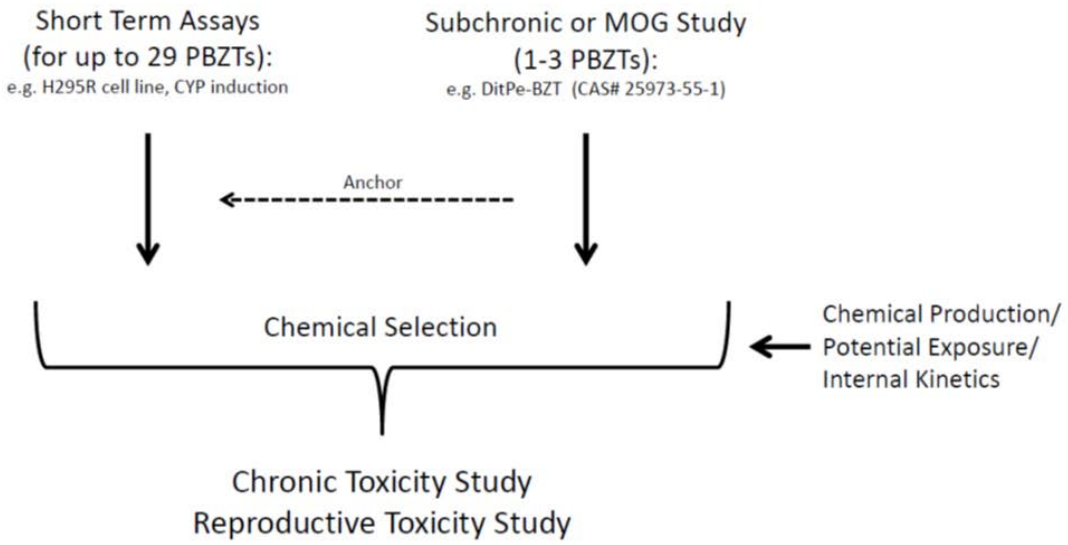
- Identifying specific potential toxicities (e.g. reproductive) and tailoring further testing to these toxicities would allow a more targeted approach to a class evaluation.

Evaluating the Class

Two Paths:

1)Evaluate the PBZTs in *in vitro* assays

2)Evaluate select PBZTs *in vivo* in a developmental exposure scenario



Specific Aims and Proposed Approach

- Evaluate the PBZTs class in short-term *in vitro* and/or *in vivo* assays to prioritize chemicals on the basis of potential toxicity and accumulation potential
  - Thirteen PBZTs (nine of the ten PBZTs with identified production) were selected for Tox21 plates
    - Some PBZTs already evaluated for activity: mostly inactive
  - Additional assays to complement Tox21 (e.g., focus on steroidogenic and CYP pathways) in order to target specific mechanisms of potential toxicity

Specific Aims and Proposed Approach

- Selected chemicals will undergo toxicity evaluation, which may include reproductive, prenatal, and subchronic toxicity evaluations in order to anchor the short term assays
  - Current in vivo data suggest reproductive, liver, and kidney toxicity
  - Select one to three chemicals for toxicity testing likely in a modified one generation design

Specific Aims and Proposed Approach

- Evaluate the ADME and PK of selected PBZTs via oral and potentially dermal routes of exposure and between males and females to better understand the influence of route of exposure and sex on internal dose

- A chronic toxicity study may be warranted based on extensive exposure and limited chronic toxicity and carcinogenicity evaluation for the class

Significance and Expected Outcome

- The presence of this class of chemicals in the environment, with the potential of accumulation, and some use in cosmetics and sunscreens requires a better understanding of the hazards associated with PBZTs.

- A class evaluation that incorporates a prioritization or ranking of hazard concerns in combination with anchoring to in vivo evaluations will aid in the risk assessment of PBZTs.

- The identification of PBZTs with a hazard concern and evaluation of pharmacokinetic parameters will also provide a basis for selecting chemicals as substitutes in products.